IN THE CLAIMS

Please cancel claims 10-19 without prejudice.

A clean version of all pending, amended and new claims is provided herewith in **Attachment C**. It will be noted that claims 1, 3, 8 and 9 have been amended relative to the previously provided version and new claims 20-22 have been added as shown by the marked up version thereof in **Attachment D** provided herewith.

REMARKS

Claims 1-9 and 20-22 stand pending in the present application. By this Amendment, claims 1 and 3 have been amended, claims 10-19, drawn to the non-elected invention, have been canceled and new claims 20-22 have been added. Applicant respectfully submits that the present application is now in a condition for allowance based on the discussion which follows.

The Examiner indicated that the present application fails to comply with the requirements of 37 C.F.R. § 1.821-1.825 for failing to include a sequence listing for nucleotide sequences disclosed within the specification. By this Amendment, Applicants have submitted a sequence listing in both paper copy and computer readable form in compliance with the requirements of 37 C.F.R. § 1.821-1.825 and further as set forth on the attached Notice To Comply With Requirements for Patent Applications Containing Nucleotide Sequences and/or Amino Acid Sequence Disclosures. Applicant further submits that the paper copy and computer readable form are the same and do not include new matter.

The specification has objected to for failing to include nucleotide acid sequence identification for several nucleic acid sequences of Figure 1. By this Amendment,

Applicants have amended the specification to provide reference to the nucleic acid sequences in Figure 1 thereby obviating the objection to the specification for failure to include sequence ID numbers for the nucleic acid sequences of Figure 1.

In addition, the specification was objected to for not providing a description for item 38 in Figure 3. With this Amendment, Applicants have provided a Letter to the Draftsperson proposing a correction to Figure 3 in which reference item 38 is removed thereby obviating the objection.

Claim 9 was objected to for failing to include a period at the end of the claim. By this Amendment, Applicant has amended claim 9 to correct this informality thereby obviating the objection to claim 9.

Claims 1-3 and 7-9 were rejected under 35 U.S.C. § 102(b) as being anticipated by Warburton et al (hereinafter "Warburton") in light of Cocuzza et al (U.S. Patent No. 5,484,701, hereinafter "Cocuzza"). By this Amendment, Applicants have amended claim 1 to more clearly recited Applicants' invention. The present invention as amended now recites selecting a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence where the sequence has no inherent secondary structure. A dideoxy sequencing reaction is prepared using the DNA template and one dideoxy nucleotide terminator to produce DNA fragments.

Warburton individually or in combination with Cocuzza fails to teach or suggest all elements of the present invention. Specifically, Warburton and/or Cocuzza fails to teach or suggest selecting a DNA template having a microlocus sequence comprising multiple copies of a nucleotide motif sequence where the sequence has no inherent secondary structure. Although the Examiner accurately indicates that during denaturing

by a high concentration of urea during the process of electrophoresis, a DNA fragment may have no secondary structure, the DNA sequence, itself, may have an inherent secondary structure prior to denaturing.

Warburton and Cocuzza fail to teach or suggest selecting a DNA sequence which has no inherent secondary structure. Warburton merely shows conventional dideoxy sequencing reaction comprising conventional chain-termination dideoxy nucleotide method of Sager and coworkers. Further, no where does Cocuzza teach or suggest a DNA sequence lacking an inherent secondary structure, let alone selecting a DNA having no secondary structure in a dideoxy sequencing reaction; Cocuzza merely discloses a method of sequencing using biotin-strepavidin conjugates to facilitate the purification of primer extension products.

Moreover, Warburton and Cocuzza fail to teach or suggest any method of selection or any benefit for selecting a DNA sequence with no inherent secondary structure. Conversely, and for exemplary purposes only, the present specification discloses that one benefit of using DNA sequences with no inherent secondary structure, is that the DNA fragments produced will move through an electrophoresis gel more consistently and less aberrantly than fragments possessing inherent secondary structure. Further, the present specification discloses the use of programs such as FOLD to calculate the inherent secondary structure of DNA using assigned energy values to the most stable intra-molecular species that can potentially form based upon the primary nucleotide sequence.

Based on the forgoing discussion, Applicants respectfully submit that claims 1-3 and 7-9 are not anticipated or made obvious by Warburton, individually or in

combination with Cocuzza and therefore Applicants respectfully request that the Examiner withdraw the rejection to claims 1-3 and 7-9 under 35 U.S.C. § 103 as being obvious over Warburton in view of Cocuzza.

Claims 1-9 were rejected under 35 U.S.C. § 102(e) or alternatively under 35 U.S.C. § 103 as being obvious over Xu et al (hereinafter "Xu") in light of Cocuzza. As noted by the Examiner, Xu discloses a method of analyzing DNA using continuous repeats of $(CCTTT/GGAAA)_n$. However, Xu fails to teach or suggest selecting a DNA template having no inherent secondary structure. Therefore Xu fails to anticipate claim 1. Cocuzza, as discussed above, also fails to teach or suggest selecting a DNA template having no inherent secondary structure.

In addition, the dependent claims recite additional novel elements not taught or suggested by Xu. For example, claim 8 recites that the motif sequence comprises a sequence with at least one unique nucleotide base. Xu fails to disclose any motif any DNA sequence comprising multiple copies of a motif sequence with one unique nucleotide base. On the contrary, the only repeated sequences disclosed in Xu are $(CCTTT/GGAAA)_n$, both motifs having repeated bases of "C", and "T", or "G" and "A".

Based on the foregoing discussion, claims 1-9 are not anticipated nor made obvious by Xu view of Cocuzza. Therefore, Applicants respectfully request that the Examiner withdraw the rejection to claims 1-9 as being anticipated under 35 U.S.C. § 102(e) or in the alternative under 35 U.S.C. § 103(a).

By this Amendment, Applicants have added claims 20-22 based on original claim 1, and which Applicants respectfully submit are allowable over the prior art of

record. Subject matter basis for added claims 20-22 can be found in the specification and claims as filed and therefore no new matter has been added.

Claim 20, depends from claim 1 and recites that the DNA fragments differ in length from one of a next shorter length and from a next longer length by one motif sequence.

Applicants respectfully submit that Warburton, Cocuzza, and Xu fail to teach or suggest using a dideoxy sequencing reaction to produce DNA fragments where each fragment differs in length from one another by a next shorter length and from a next longer length by one motif sequence.

Warburton merely shows a conventional dideoxy sequencing reaction comprising conventional chain-termination dideoxy nucleotide method of Sager and coworkers. Specifically, Warburton is directed to PCR amplification of tandemly repeated DNA. Warburton uses alpha satellite DNA consisting of approximately 171 bp monomer which is tandemly repeated to form arrays as large as several thousand kb (Warburton, page 6033, column 2). Warburton then uses polymerase chain reaction (PCR) to amplify alpha satellite DNA (Warburton, page 6034, first column). Direct sequencing was performed on the PCR amplified chromosome 17 alpha satellite DNA as shown in Warburton Figure 2.

The fragments generate by any one of Warburton's four sequencing reactions, one for dideoxy GTP, CTP, TTP and ATP as shown in Figure 2, differ by the number of bases between each respective nucleotide base, one nucleotide base, not by one motif sequence length as claimed. Therefore, Warburton fails to teach or suggest producing

DNA fragments each differing in length from one another by one motif sequence as claimed.

Further, Cocuzza fails to teach or suggest preparing a dideoxy sequencing reaction to produce fragments each of which differ in length from one of a next shorter and a next longer fragment by one motif sequence. Cocuzza is directed to a method of sequencing using biotin-strepavidin conjugates to facilitate the purification of primer extension products. No where does Cocuzza teach or suggest producing DNA fragments differing in length by one motif sequence.

In addition, Xu fails to teach or suggest preparing a dideoxy sequencing reaction using a DNA template to produce DNA fragments each different in length from one another by the motif sequence length. Moreover, using the motifs of Xu, it would not be possible to produce DNA fragments differing in length by motif sequence using a dideoxy sequencing reaction. For example, as taught in the present invention, in order to use a dideoxy sequencing reaction with a DNA template comprising multiple copies of a motif to produce DNA fragments each different in length by the motif sequence, the motif sequence must include a single unique nucleotide base such that during sequencing, dideoxy termination occurs at that unique base which terminates the motif, thereby producing DNA fragments of lengths which differ by one motif sequence. As discussed above, none of repeated DNA sequences of Xu include a unique nucleotide base.

Based on the foregoing discussion, Applicants respectfully submit that claim 20 is not anticipated by or obvious from the prior art of record.

Added claims 21-22 are directed to a method of producing a DNA size standard by selecting a DNA template comprising multiple copies of a nucleotide motif sequence where the nucleotide motif sequence has exactly one unique nucleotide base. A dideoxy sequencing reaction is prepared using the DNA template to produce DNA fragments. In claim 22 the fragments differ in length by that of one motif sequence.

Applicants respectfully submit that the prior art of record fails to teach or suggest selecting a DNA template comprising multiple copies of a nucleotide motif sequence where the nucleotide motif sequence has exactly one unique nucleotide base. As discussed above with reference to the prior art rejection to claim 8, Xu and Cocuzza fail to teach or suggest selecting a DNA template comprising multiple copies of a nucleotide motif sequence where the nucleotide motif sequence has exactly one unique nucleotide base. Similarly, Warburton is silent as to a repeated DNA motif having a unique nucleotide base, let alone selecting a DNA template having multiple copies of a motif in which the motif has a unique nucleotide base.

Based on the foregoing discussion, Applicant respectfully submits that added claims 21-22 are novel and not obvious over the prior art of record.

In view of the foregoing, Applicant submits that the present application is now in a condition for immediate allowance and indication of such is respectfully solicited.

Should the Examiner for whatever reason find the application in anything but a condition for allowance, the Examiner is invited to call the undersigned at the number below.

Respectfully submitted,

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July 9, 2002

ATTACHMENT B

Marked Up Replacement Paragraphs/Addition of Sequence Listing

At the following locations, a marked up copy of the replaced paragraph and a new sequence listing is provided.

Pages 5-6, paragraph no. [0022]:

[0022] Referring now to Figure 1, a double standard DNA sequence, denoted 10 and having a sense strand sequence of SEQ ID NO: 1, is ~~show~~ shown which comprises a microsatellite locus 12. DNA sequence 10 is a basic sequence used for illustrative purposes and is used to simplify the explanation of the present invention.

Page 6, paragraph no. [0023]:

[0023] Microsatellite locus 12 (SEQ ID NO: 2) is composed of five copies of CA (SEQ ID NO: 3) nucleotide motif sequence 14. Unique DNA sequences (i.e. non-motif, repeating sequences) flank both the 5' and 3' ends of the microsatellite locus 12. In the example illustrated, DNA sequence TCGAGGGTATCATGTT (SEQ ID NO: 4) flanks the 5' end and DNA sequence GTTAGGG (SEQ ID NO: 5) flanks the 3' end of microsatellite locus 12.

Page 6, paragraph no. [0025]:

[0025] In general, DNA is composed of two antiparallel complementary strands. During DNA synthesis primed by primer 9 (SEQ ID NO: 6) in this example, the upper strand is displaced and the lower strand is used as template with the complement (C pairs with G; A with T) of each base of the lower strand being sequentially added

thereby synthesizing a new upper strand in the 5' to 3' direction. A dideoxy DNA sequencing reaction is prepared using DNA template 10. The sequencing reaction includes a primer, and the four deoxynucleotide triphosphates, dATP, dCTP, dGTP, and dTTP. In addition, the sequencing reaction includes dideoxy ATP (ddATP). The primer is labeled with a fluorescent tag, but could also be labeled by other means (e.g., radioactive tag, IR tag, etc.). The sequencing reaction is allowed to proceed (as indicated by arrow 16) to synthesize a two nucleotide ladder DNA size standard denoted 18.

Page 7, paragraph no. [0029]:

[0029] At the conclusion of the DNA sequencing reaction, DNA size standard 18 is produced. DNA size standard 18 comprises five DNA fragments 20, 22, 24, 26 and 28 (SEQ ID NOS: 7-11, respectively) formed of the primer, 5' flanking sequences and two to five copies of motif sequence 14, respectively. As shown, DNA fragments 20, 22, 24, 26 and 28 are 18, 20, 22, 24, and 26 nucleotides in length, respectively.

marked paragraphs

After page 10, insert the following sequence listing:

SEQUENCE LISTING

<110> DOI-USGS
Bucholz , Wallace

<120> High Resolution DNA Size Standards

<130> FWS-3679

<140> US 09/909,806
<141> 2001-07-16

<160> 11

<170> PatentIn version 3.1

<210> 1
<211> 33
<212> DNA
<213> unidentified

<400> 1
tcgagggtat catgttcaca cacacagtta ggg 33

<210> 2
<211> 10
<212> DNA
<213> unidentified

<400> 2
cacacacaca 10

<210> 3
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<400> 3

ca 2

marked paragraphs

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marked paragraphs

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tcgagggtat catgttcaca cacaca 26

ATTACHMENT C

Clean Replacement/New Claims (Entire Set Of Pending Claims)

Following herewith is a clean copy of the entire set of pending claims.

1. (Amended) A method of producing DNA size standards, said method comprising the steps of:

A6 selecting a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence and where the sequence has no inherent secondary structure; and

preparing a dideoxy sequencing reaction using the DNA template and one dideoxy nucleotide terminator.

2. The method of claim 1, wherein the dideoxy nucleotide is selected from the group consisting of dideoxy ATP, dideoxy GTP, dideoxy CTP, dideoxy TTP and any analog thereof that can terminate the sequencing reaction.

3. (Amended) The method of claim 1, wherein DNA fragments produced by A1 the dideoxy sequencing reaction lack inherent secondary structure.

4. The method of claim 1, wherein the motif sequence is one of a group consisting of two to six nucleotides.

5. The method of claim 1, wherein the DNA template comprises n copies of the motif sequence, wherein n is an integer from 10 to 200.

6. The method of claim 4, wherein the DNA template comprises n copies of the motif sequence, wherein n is an integer from 10 to 200.

7. The method of claim 1, wherein the DNA template comprises a microsatellite locus.

8. The method of producing a DNA size standard of claim 1, wherein the motif sequence comprises a sequence with one unique nucleotide base.

9. (Amended) The method of producing a DNA size standard of claim 1, wherein the dideoxy sequencing reaction produces DNA fragments comprising a respective number of copies of the motif sequence.

10. (Canceled)

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. (New) The method of claim 1, wherein each one of the DNA fragments differ in length from one of a next shorter length and from one of a next longer length by one motif sequence.

21. (New) A method of producing DNA size standards, said method comprising the steps of:

selecting a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence, the nucleotide motif sequence having exactly one unique nucleotide base;

preparing a dideoxy sequencing reaction using the DNA template and one dideoxy nucleotide terminator corresponding to the unique nucleotide base to produce DNA fragments.

22. (New) The method of claim 21, wherein each one of the DNA fragments differ in length from one of a next shorter length and from one of a next longer length by one motif sequence.

ATTACHMENT D

Marked Up Replacement/New Claims

Following herewith is a marked up copy of each rewritten claim together with all other pending claims.

1. (Amended) A method of producing DNA size standards, said method comprising the steps of:

selecting ~~providing~~ a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence and where the sequence has no inherent secondary structure; and

preparing a dideoxy sequencing reaction using the DNA template and one dideoxy nucleotide terminator.

2. The method of claim 1, wherein the dideoxy nucleotide is selected from the group consisting of dideoxy ATP, dideoxy GTP, dideoxy CTP, dideoxy TTP and any analog thereof that can terminate the sequencing reaction.

3. (Amended) The method of claim 1, wherein DNA fragments produced by the dideoxy sequencing reaction lack inherent secondary structure.

4. The method of claim 1, wherein the motif sequence is one of a group consisting of two to six nucleotides.

5. The method of claim 1, wherein the DNA template comprises n copies of the motif sequence, wherein n is an integer from 10 to 200.

6. The method of claim 4, wherein the DNA template comprises n copies of the motif sequence, wherein n is an integer from 10 to 200.

7. The method of claim 1, wherein the DNA template comprises a microsatellite locus.

8. The method of producing a DNA size standard of claim 1, wherein the motif sequence comprises a sequence with ~~at least~~ one unique nucleotide base.

9. (Amended) The method of producing a DNA size standard of claim 1, wherein the dideoxy sequencing reaction produces DNA fragments comprising a respective number of copies of the motif sequence.

10. (Canceled)

11. (Canceled)

12. (Canceled)

13. (Canceled)

14. (Canceled)

15. (Canceled)

16. (Canceled)

17. (Canceled)

18. (Canceled)

19. (Canceled)

20. (New) The method of claim 1, wherein each one of the DNA fragments differ in length from one of a next shorter length and from one of a next longer length by one motif sequence.

21. (New) A method of producing DNA size standards, said method comprising the steps of:

selecting a DNA template having a sequence comprising multiple copies of a nucleotide motif sequence, the nucleotide motif sequence having exactly one unique nucleotide base;

marked claims

preparing a dideoxy sequencing reaction using the DNA template and one dideoxy nucleotide terminator corresponding to the unique nucleotide base to produce DNA fragments.

22. (New) The method of claim 21, wherein each one of the DNA fragments differ in length from one of a next shorter length and from one of a next longer length by one motif sequence.

marked claims